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Drug abuse: another challenge for the cardiologist?

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Abstract

The abuse of illicit drugs is a major social and health problem. In fact, illicit drugs are responsible of many adverse systemic effects which may require urgent medical treatment. In the present review we report details on the prevalence of the major illicit drugs abused in Europe in 2009, according to the report of the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA), focusing on the effects on the cardiovascular system, including sudden cardiac death.

Epidemiology of illicit drug abuse in Europe

The abuse of illicit drugs is a major social and health problem. In fact the United Nations Observatory (UNODC) ¹ reports that in 2009 between 3.3% and 6.1% of the worldwide population aged 15-64 admitted to have used illicit substances at least once during the previous year. Based on the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA)², Europe is attributed a similar prevalence of drug abuse, and quotes, following the past decades reporting amazing raises, seem unfortunately stable.

In details, Cannabis is by far the most frequently abused illicit substance (Figure 1). Lifetime prevalence is 10% to 30% of the population aged 15-64, and 6.7% in this age range used it at least once in 2009 in Europe². Cannabis use is mainly concentrated among young people (15-34 years) in which the prevalence is 12.1% during 2009. Males are most likely to use this substance than females, while Italy, Czech Republic and Spain are the countries with the highest prevalence of abusers.

Cocaine is the second most used drug in Europe, with a lifetime prevalence of 4.3% among population aged 15-64 and 5.9% among population aged 15-34. Its last-year prevalence is estimated 1.2% of the population aged 15-64 and 2.1% of the population aged 15-34. Also concerning this substance males are more frequently users than females, with higher prevalence in Spain, UK, Italy and Ireland. Of note, cocaine is often used in association with other illicit drugs, especially cannabis and alcohol. Among synthetic recreational drugs, amphetamines and ecstasy (3,4-methylenedioxy-methamphetamine, MDMA) are the most commonly nowadays abused in Europe. Besides these, new synthetic stimulant and hallucinogenic drugs are continuously spreading worldwide especially among young people for their psychotropic effects including mood elevation, increased emotional sensitivity and closeness to others. Amphetamines use in 2009 is estimated in Europe about 0.5% of the population aged 15-64 and 1.1% of the population aged 15-34, and their use is larger in UK and

Northern Europe. Their estimated lifetime use in European population aged 15-64 is 3.8%.

Concerning ecstasy, estimates of lifetime prevalence are 3.2% among the population aged 15-64, while last-year prevalence is 0.7% of the population aged 15-64 and 1.4% of the population aged 15-34. Its use is more frequent in UK, Ireland, Czech Republic and Slovakia. Eventually heroin and other opiates remain a social problem in European countries, although use is decreasing due to the fear of diseases transmittable by syringes, like AIDS and hepatitis. Estimates of their lifetime prevalence are less reliable compared to other substances, but should roughly reach about 4 people per 1000 population aged 15-64, with a similar last-year prevalence among population aged 15-64 and 15-34. Despite the low prevalence, however, these drugs are strongly problematic because of their strong physical and psychological dependence, and the frequent medical complications related to their use.

Aiming to estimate the diffusion of these substances among students, the European School Survey Project on Alcohol and Other Drugs (ESPAD)³ reports that 18% of students aged 15-16 years have used illicit drugs at least once in their life, mainly Cannabis (13%) but also other substances such as cocaine and synthetic recreational drugs (6%), highlighting the important diffusion of this phenomenon among the youngest.

Cardiovascular toxicity of illicit drugs

Illicit drugs are responsible of many adverse systemic effects, which may require urgent medical treatment. In the following we focus on their effects on the cardiovascular system (Table 1).

Cannabis

Cannabis is usually smoked and rapidly absorbed through the lung. Its absorption is slow and variable, for this reason its effects are less predictable than other abuse substances. The toxic

potential of cannabis is generally considered low, but the wide diffusion and consistent use of this substance as a recreational drug determines considerable adverse effects^{4,5}. Although the most frequent are neurological side effects, the cardiovascular system is also affected due to the biphasic effect on the autonomic nervous system. At low or moderate doses cannabis increases sympathetic activity and reduces parasympathetic activity, while at high doses leads to the opposite effect, with a parasympathetic activation and sympathetic inhibition⁶. Cannabis, as a consequence of the effect on action potentials and refractory periods durations⁷ in the atria, favors automaticity, triggered activity and micro-re-entry^{8,9} leading to atrial arrhythmias such as premature contractions, atrial flutter or fibrillation¹⁰. Cannabis may also lead to ventricular premature contractions and ST-T segment alterations on ECG¹¹. Due to an interference with the integrity of the peripheral vascular reflex responses which protect myocytes from ischaemia, and coronary vasospasm, also a few cases of acute myocardial infarction have been associated to cannabis use¹². Eventually peripheral arteritis¹³, similar to Burger disease, may be found in heavy cannabis smokers. Of note, all these cardiovascular effects are potentiated when cannabis is assumed with other substances as cocaine, alcohol or amphetamines.

Cocaine

Cocaine is quickly absorbed from all mucous membranes of the body, so it can be smoked, injected or most frequently inhaled. Its systemic toxicity, especially neurological and cardiovascular, is well known and largely described. Its effects on the cardiovascular system are mediated by the inhibition of catecholamine reuptake at sympathetic nerve terminals, the stimulation of central sympathetic outflow and the increased sensitivity of adrenergic nerve terminals to noradrenalin^{14,15}. By increasing blood pressure and heart rate, prolonged use induces left ventricular hypertrophy¹⁶ and premature atherosclerosis¹⁷. Cocaine also promotes vasoconstriction and thrombosis through the enhanced release of endothelin-1¹⁸, fibrinogen and von Willebrand factor¹⁹, the inhibition of nitric

oxide synthesis²⁰, and the promotion of platelets activation and aggregation²¹, provoking an increased risk of acute myocardial infarction, even in users without atherosclerotic plaques^{22, 23, 24}. Cocaine has also been involved in the development of myocarditis²⁵, myocyte necrosis²⁶ and spontaneous aortic or coronary dissections²⁷. Cardiac arrhythmias²⁸ due to a direct action on ionic channels^{29, 30} are another relevant effect of cocaine abuse. Cocaine inhibits voltage-gated Nav1.5 sodium channels³¹, leading to a reduction in myocardial conduction velocity³² and prolongation of QT interval on the ECG³³, a risk factor for ventricular arrhythmias such as ventricular tachycardia and torsades de pointes^{30, 34}. Cocaine also blocks potassium channels hERG³⁵, which are responsible for I_{Kr} repolarizing current³⁶, resulting in a complex electrophysiological substrate predisposing to cardiac arrhythmias; these effects may obviously also precipitate latent pro-arrhythmic genetic alterations such as Long-QT³⁷ and Brugada Syndromes³⁸. In addition, cocaine abusers often assume alcohol aiming to slow cocaine's metabolism and prolong the psychotropic effects. The combination of cocaine and ethanol leads to the formation of a metabolite, cocaethylene, which by itself slows cardiac conduction, delays repolarization and strongly inhibits both Nav1.5 sodium and hERG potassium channels^{39, 40}. Cocaethylene inhibition of cardiac ion channels is in fact the main cause of the increased incidence of arrhythmias associated with the combined use of cocaine and alcohol⁴¹.

Amphetamines and ecstasy

Ecstasy, or MDMA, is a synthetic derivative of amphetamine which can be assumed orally as pills. The main adverse effects of this drug are neurological, related to the release of serotonin, dopamine and noradrenalin from the monoamine neurons⁴², leading to a long-term depletion of these neurotransmitters. Effects begin after about 30 minutes and can last up to 5-6 hours after assumption. Concerning cardiovascular toxicity, complications are mainly related to a sympathetic stimulation, leading to an increase in blood pressure and heart rate. The induced vasospasm and

thrombosis, in part also mediated by an indirect effect of toxic metabolites⁴³, may cause acute myocardial infarction, supraventricular or ventricular arrhythmias and sudden cardiac death^{44, 45}.

Another recently discovered mechanism is the activation of 5-HT_{2B} serotonergic receptors, possibly leading to pulmonary hypertension and valvular heart disease⁴⁶.

Amphetamine and methamphetamine are assumed orally, but can also be inhaled or injected. These substances present neurological toxicity and several dangerous cardiovascular responses⁴⁷ due to sympathetic activation. Myocardial infarction may be secondary to vasospasm and thrombosis^{45, 48}, and sudden cardiac death to cardiac arrhythmias induced both directly and through long-lasting metabolites^{47, 49}. As for **other** abuse substances, amphetamine's toxicity is strongly potentiated by concomitant alcohol intake⁵⁰.

Stimulant and hallucinogenic drugs

Eventually hallucinogenic substances, in particular d-Lysergic Acid Diethylamide (LSD) and psilocybin are ingested orally. Their mechanisms of action, lasting about 4-5 hours, are complex and include agonist, partial agonist, and antagonist effects at various serotonin, dopamine and adrenergic receptors, leading to important neurologic and psychotropic effects⁵¹. The adrenergic effects are usually mild, lower than what can occur after taking cocaine, amphetamine or ecstasy. Cardiovascular complications are rarely serious, although occasional **attacks of supraventricular tachyarrhythmias and myocardial infarction due to serotonin induced platelet activation and sympathetic induced arterial vasospasm⁵² have been reported.**

Heroin

Heroin (diacetylmorphine) is a semisynthetic analogue of morphine, which is slowly metabolized to morphine after its assumption, and rapidly produces a well-recognized syndrome of euphoria, miosis, respiratory and central nervous system depression, due to the increase in parasympathetic

activity. Cardiovascular effects are common as a consequence of the action on the vasomotor centre provoking bradycardia and hypotension. Drug-induced bradycardia along with enhanced automaticity can induce ectopic activity, atrial fibrillation, idioventricular rhythm, or potentially lethal ventricular tachyarrhythmias⁵³.

Other opiates

Other opiates (such as dextropropoxyphene) have additional sodium channel blocking effects, which further contribute to the proarrhythmic⁵⁴ and myocardial depressant⁵⁵ effects, leading to acute left ventricular dysfunction and pulmonary oedema. Overdose of narcotic analgesics can also cause non-cardiogenic pulmonary oedema⁵⁶ secondary to several reasons (anaphylactic reaction to the drug, increase in pulmonary capillary hydrostatic pressure by hypoxia induced pulmonary vasoconstriction, alveolar capillary membrane disruption).

Drug abuse and sudden cardiac death: current literature

Sudden cardiac death (SCD) is a death occurring within an hour of the onset of symptoms⁵⁷.

Epidemiological data are related to the prevalence of coronary heart disease, its major cause. The proportion of SCD within all deaths is estimated about 13%, with an incidence in Europe between 0.36 to 1.28 per 1000 inhabitants per year^{57, 58}.

As previously stated, the majority of SCDs are related to coronary artery disease, but other relevant reasons may be cardiomyopathies or genetic arrhythmogenic diseases, such as channelopathies (Brugada, Long-QT and Short-QT Syndromes). Many SCDs unfortunately remain unexplained, especially those within young subjects without a clear predisposing substrate; given the above reported epidemiology **and the mentioned cardiovascular toxicity evidences of drug abuse**, some of them may be attributed to illicit drugs. In fact, the UNODC reports between 23.1 and 58.7 deaths

per million inhabitants aged 15-64 due to illicit drug abuse worldwide, and about a half of them are SCDs¹.

In Europe, the average mortality rate due to overdose of illicit drugs is estimated between 4 and 59 deaths per million population aged 15–64 years (Figure 2). The majority of these deaths are among young people, with a median age of about 35 years, and often present as SCDs². Frequently a poly-drug abuse is involved, especially when heroin is associated with cocaine, ethanol or benzodiazepines^{59, 60}.

The real prevalence of SCDs due to drug abuse has not been systematically assessed in large studies, but many reports of fatalities in abusers have been published (Table 1).

As mentioned before, cannabis has a relatively low toxic potential, but a few cases of SCD have been reported after cannabis assumption, both alone^{61, 62} than associated with other drugs such as cocaine or amphetamines^{63, 64}.

A wider body of evidence is available instead on cocaine. Cocaine has the potential to provoke cardiac arrest through many mechanisms, therefore cases of massive myocardial infarction due to coronary thrombosis or vasospasm⁶⁵, acute aortic or coronary dissection²⁷, acute systemic thrombosis⁶⁶ and ventricular arrhythmias, leading to ventricular fibrillation and SCD may be found. Twenty-two cases of cardiac arrest after crack cocaine smoking are reported by Hsue et al.⁶⁷. In a large Spanish study cocaine use has been associated with 3% of total SCDs⁶⁸, and another study suggested a 6-fold higher risk for SCD in cocaine abusers compared to the general population⁶⁹. Darke et al. reported 83 cocaine-related cardiovascular deaths over 146 cocaine-related fatalities⁷⁰. Cases of asystole and ventricular fibrillation^{71, 72, 73} have also been reported related to the induction of Brugada patterns on the ECG^{74, 75} or torsades de pointes in patients with known Long-QT Syndrome³⁷. Despite the common induction of tachyarrhythmias as cause of SCD in cocaine users, also a case of syncope related to bradyarrhythmia⁷⁶ has been reported. The contemporary

assumption of other drugs, especially heroin^{70, 77}, or ethanol⁷⁸, can potentiate these effects, leading to a higher risk of sudden fatalities.

Amphetamine, methamphetamine and MDMA have also been implicated in some cases of SCD, both alone^{79, 80, 81, 82, 83} than in association with cocaine or alcohol⁸⁴.

Obviously heroin can lead to SCD^{85, 86, 87} through the depression of respiratory and cardiovascular centres in the central nervous system, causing asystole and cardiac arrest. In fact, despite its lower prevalence compared to other drugs, heroin abuse is frequently related to life threatening complications.

How to face the challenge?

Given the epidemics of drug abuse together with the evidence of the related cardiovascular toxicity, illicit substances should necessary be searched for at least within **young adults with cardiovascular disorders**. The majority of drugs of abuse present a short half-life, but their use can be traced through their metabolites, with much longer half-lives than the primitive substance.

Cannabis (whose active component is Δ 9-tetrahydrocannabinol) has a plasma half life of 20–30 hours and can be detected in urine for several days in occasional users, and for up to two months in heavy users^{88, 89}. Cocaine has a short serum half life (30–80 minutes), and is mainly metabolized and excreted in urine over a two week period, so its metabolites (the most important are benzoilecgonine and ecgonine methyl-ester) are reliable markers of a recent **assumption**⁸⁸. Another metabolite, cocaethylene, presents a half-life of several days and is useful to detect the dangerous concomitant **assumption** of cocaine and alcohol. Amphetamine, methamphetamine and their metabolites (in particular methylenedioxy-amphetamine) can be detected in urine for several days after **assumption**, and their excretion is prolonged after administration of larger doses or in the

presence of alkaline urines⁸⁸. MDMA is metabolized by the liver and excreted by the kidney for several days after assumption, so its recent use is easily traceable in the urine, both in its native form than through metabolites⁸⁸. Morphine (the main heroin active metabolite) has a plasma half-life of 2-3 hours and undergoes rapid hepatic metabolism. Metabolites are excreted in urine, and despite duration of renal excretion is highly variable and affected by the dose, chemical composition of street preparations, user's previous drug habits, and individual variations in renal and hepatic function, they may be detected for up to 48 hours in occasional users and several days in chronic users⁸⁸.

All the aforementioned substances can also be traced using hair analysis, which provides a longer window of detection, typically 1 to 3 months according to the substance examined⁹⁰, compared to urine analysis. Hair analysis, in fact, provides a very useful tool to search for long-term abuse⁹¹, but is surely more expensive than urine analysis that remains the most valid option to trace recent, acute substance assumption⁹².

Previous experiences using systematic toxicological screening have in fact provided interesting results. Lucena et al.⁶⁸ in an autoptic study on 668 population, analyzed blood and urine samples searching for cocaine, benzoilecgonine, cocaethylene, methylenedioxy-amphetamine (an amphetamine metabolite), MDMA, morphine, Δ 9-tetrahydrocannabinol (cannabis), and ethanol. Cocaine metabolites and cocaethylene were present in about 3% of the total population, suggesting a non irrelevant role of drug abuse in SCDs.

Conclusion

Illicit drug abuse is common in Europe and most probably underestimated, especially among young adults. Recognize, treat and possibly prevent the adverse effects of these substances, which may lead to important cardiovascular and systemic complications, should become an aim for the cardiologist. For this reason, we suggest toxicological screening protocols with urine analysis, and

possibly hair analysis, for young adults with cardiovascular disorders and without recognizable structural or functional cardiac diseases, focusing at least on the most frequently abused and most toxic substances. By this approach a more precise definition of the risk profile of each illicit drug may be drawn and public health initiatives preventing specific illicit drug abuse may be improved. Furthermore evidence of drug abuse as a cause of aborted SCD may surely help to direct therapeutic options (e.g. implantable cardiac defibrillator) only to those individuals proving the ability to stop their addiction.

Table 1. Commonly abused substances in Europe with side effect's mechanisms, major cardiovascular complications and reported sudden cardiac deaths.

Substance	Mechanisms	Cardiovascular complications	Reported SCDs
Cannabis	Biphasic: sympathetic-like at low doses parasympathetic-like at high doses	Supraventricular arrhythmias Hypotension, bradycardia	Ref. 9, 61, 62, 63, 64.
Cocaine	Inhibits reuptake of catecholamines Sympathetic-like Blocks Na ⁺ (Nav1.5) channels Blocks K ⁺ (hERG) channels	Hypertension, left ventricular hypertrophy Vasospasm, thrombosis and myocardial infarction Atrial and ventricular arrhythmias Myocarditis and necrosis	Ref. 27, 28, 37, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 77.
Amphetamine	Release of dopamine and noradrenalin (sympathetic-like)	Vasospasm, thrombosis and myocardial infarction Arrhythmias	Ref. 69, 79, 80, 81, 83.
Ecstasy	Release of serotonin, dopamine and noradrenalin (sympathetic-like)	Vasospasm, myocardial infarction Arrhythmias Pulmonary oedema	Ref. 44, 49, 69, 82, 84.
Hallucinogenic drugs	Serotonergic, dopaminergic and adrenergic activity	Hypertension Arrhythmias Vasospasm, myocardial ischemia	Ref. 51, 52.
Heroin - opiates	Vasomotor centre depression (parasympathetic-like) Histamine release	Bradyarrhythmias, hypotension Supraventricular and ventricular arrhythmias Pulmonary oedema	Ref. 59, 60, 77, 85, 86, 87.

Figure 1. Estimated lifetime prevalence (aged 15-64: black bars) and last-year (2009) prevalence among different population groups (aged 15-64: grey bars; aged 15-34: white bars) of the most commonly used illicit substances. Adapted from Ref. 2.

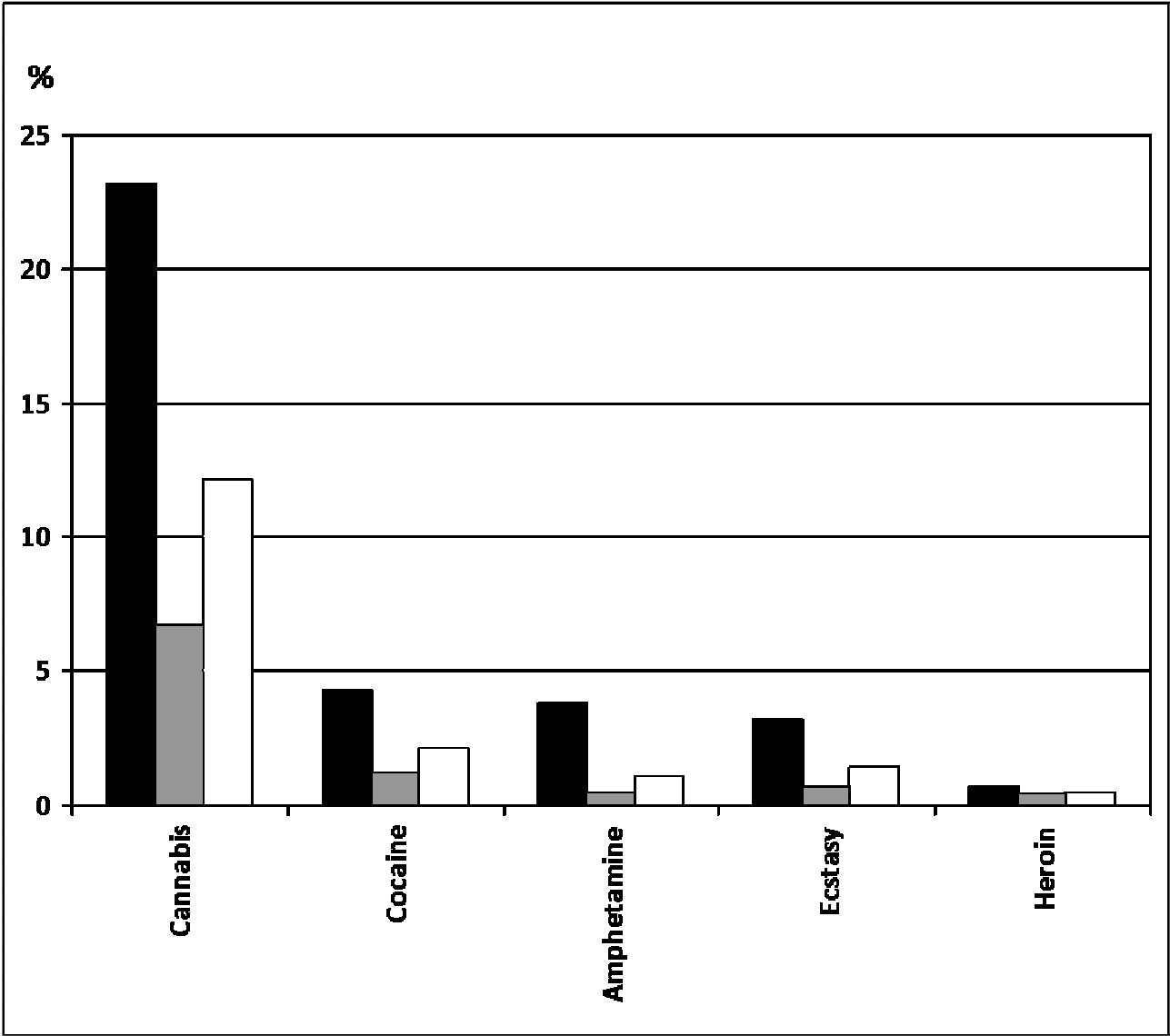
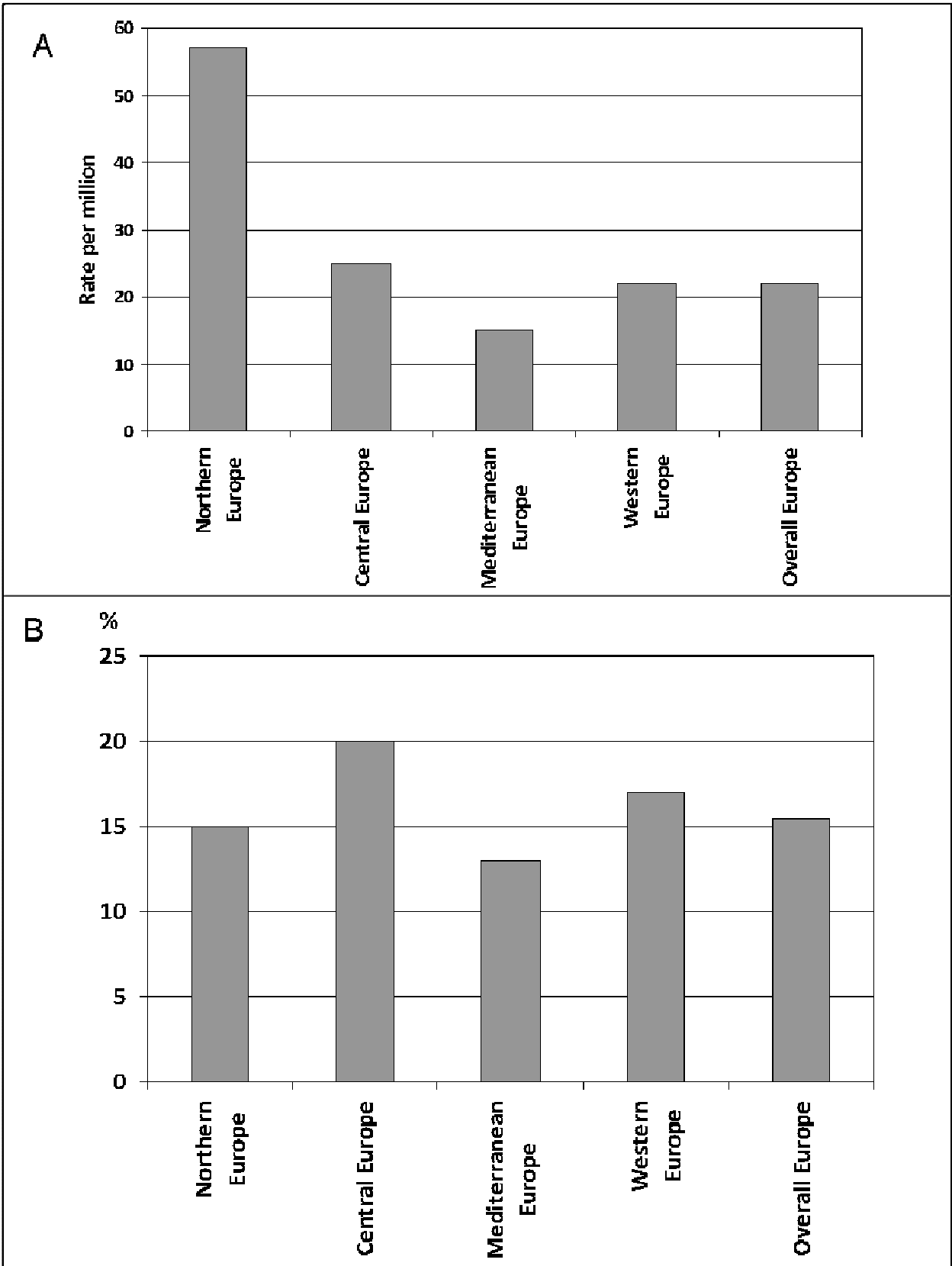


Figure 2. Estimated drug-induced deaths per million inhabitants among all adults aged 15-64 in Europe in 2009 (A) and estimated percentage of drug-related deaths among all deaths occurring in the population up to the age of 24 years (B). Adapted from Ref. 2.



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